Special Article

[We are publishing this Special Article to commemotare World Hepatitis Day on 28th July]

Operational Guidelines of NVHCP for management of Hepatitis B

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Viral Hepatitis is a global public health problem with deaths comparable to that caused by tuberculosis or HIV. Infection can be caused by the five known hepatitis viruses- A,B,C,D and E.While, Hepatitis B and C are transmitted by exchange of blood and other body fluids other virus like Hepatitis A and E are transmitted mainly byfaeco oral route.

Viral hepatitis is increasingly being recognized as a public health problem in India.National Viral Hepatitis Control Program aims to combat hepatitis and achieve country wide elimination of Hepatitis C by 2030. This program also aims to achieve significant reduction in the infected population, morbidity and mortality associated with Hepatitis B and C like cirrhosis and hepatocellular carcinoma (liver cancer). NVHCP also aims to reduce the risk, morbidity and mortality due to Hepatitis A and E.

This article describes the scope of this program with special reference to the management of Hepatitis B.

[*J Indian Med Assoc* 2021; **119(7):** 83-8]

Key words **: Viral Hepatitis, Hepatitis B, NVHCP, Hepatitis B Immunization.**

Viral hepatitis is a global public health problem of epidemic proportions that caused 1.34 million deaths in 2015 and is comparable to deaths caused by tuberculosis and higher than those caused by HIV. Infection can be caused by the five known hepatitis viruses – A, B, C, D and E (HAV, HBV, HCV, HDV and HEV). Many of these infections are preventable. Hepatitis B and C are responsible for 96% of overall hepatitis mortality.

World Hepatitis Day - 28th July

Hepatitis B and C are transmitted by unsafe injection practices& through contaminated syringes and needles, infected blood and blood products, sexual transmission, from infected mother to child. Globally, in 2015, an estimated 257 million people were living with chronic HBV infection, and 71 million people with chronic HCV infection.

Viral hepatitis is increasingly being recognized as a public health problem in India. In the general population, Hepatitis B surface Antigen (HBsAg) positivity ranges from 1.1% to 12.2%, with an average prevalence of 3-4% In India, approximately 40 million people are chronically infected with Hepatitis B Chronic HBV infection accounts for 40% of Hepato-cellular Carcinoma (HCC) and 20-30% cases of cirrhosis in India.

The Government of India is a signatory to the resolution 69.22 endorsed in the WHO Global Health Sector Strategy on Viral Hepatitis 2016-2021 at 69th WHA towards ending viral hepatitis by 2030. Thus was introduced the National Viral Hepatitis Control Program (NVHCP).

This article describes the scope of this program with special reference to the management of Hepatitis B.

Editor's Comment :

- Hepatitis B Immunization, safety of blood products and promotion of behavioral change regarding use of condom, single use of needles are important keys in prevention of transmission of Hepatitis B.
- Acute and Chronic Hepatitis B may be determined by the assessment of Serological Markers.
- Management Hepatitis B depends upon the serological markers of HBV infection, measurement of HBV DNA levelsand assessment of severity of liver disease by -Liver enzymes, Non-invasive tests (NITs) such as aspartate aminotransferase (AST)-to-platelet ratio index (APRI), FIB-4, transient elastography (FibroScan) or Liver biopsy.
- A Chronic HBsAg positive patient with cirrhosis clinically or APRI >2 or FIB4 >3.25 is to be treated with Tenofovir disoproxil fumarate (TDF) 300 mg once daily or Entecavir (adult with compensated 0.5 mg liver disease and lamivudine naive) once daily or Entecavir (adult with decompensated 1 mg liver disease) once daily or Tenofovir alafenamide 25 mg fumarate (TAF) once daily.
- Monitoring of treatment is done bymonitoring for disease progression and treatment response in persons with CHB prior to, during and posttreatment;looking for tenofovir or entecavir side-effects and monitoring for hepatocellular carcinoma.

NVHCP

Aim :

(1) To combat hepatitis and achieve country wide elimination of Hepatitis C by 2030

(2) To achieve significant reduction in the infected population, morbidity and mortality associated with

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Hepatitis B and C viz, cirrhosis and hepatocellular carcinoma (liver cancer)

(3) To reduce the risk, morbidity and mortality due to Hepatitis A and E.

Key objectives :

(1) To enhance community awareness on hepatitis

(2) To provide early diagnosis and management of viral hepatitis at all levels of healthcare

(3) To develop standard diagnostic and treatment protocols for management

(4) To strengthen the existing infrastructure facilities and human resource

(5) To develop linkages with the existing National programmes

(6) To develop a web-based "Viral Hepatitis Information and Management System" to maintain a registry of persons affected with viral hepatitis and its sequelae.

Components :

The key components include:

1. Preventive component :

2. Diagnosis and Treatment :

3. Monitoring and Evaluation, Surveillance and Research

4. Training and capacity Building

Program management :

The NVHCP is coordinated by the units at the centre and the states.

(1) National Viral Hepatitis management unit (NVHMU)

(2) State Viral Hepatitis management unit (SVHMU)

(3) District Viral Hepatitis management unit (DVHMU)

Firstly key populations or high-risk groups (HRGs) under the National Viral Hepatitis Control Program have been designated. All key and bridge population groups under the NACP for HIV infections are specially vulnerable to viral hepatitis infections too .

High Risk Groups are :

(1) Recipients of multiple blood/blood products transfusion (especially before implementation of hepatitis C testing at a large scale in India; ie, before 2001)

(2) Patients on haemodialysis

(3) People Who Inject Drugs

(4) Male having sex with male (MSM)

(5) Female sex workers

(6) Sexual partners of infected people

(7) Prisoners, migrant workers and truck drivers

(8) Close first degree relatives and family members: mother, siblings, spouse and children, of persons affected with viral hepatitis.

India's target for Hepatitis B immunization

Sl No	Country Targets (to be provided by UIP)	Baseline 2019-20 (2016-17)	
1.	Coverage of Birth Dose of Hepatitis B (All deliveries)		90%
2.	Coverage with three doses of Hepatitis B vaccine in infants (B3).		95%
3.	Routine Hepatitis B vaccination among health-care workers.	N/A	Will be made Available

Safety of blood and blood products :

- Strengthening of blood safety is necessary as HBV and HCV can be transmitted through contaminated blood and blood products.
- it is compulsory to screen every unit of blood for HBV and HCV along with other transfusion transmitted infections (TTIs) before transfusion, in all licensed blood banks.
- Screening for HCV was made mandatory and introduced in 2001 across blood banks in India.

Harm reduction in key populations :

- To provide a package of prevention services including behavioural change communication, condom promotion, prevention and management of sexually transmitted infections (STI), community mobilization and enabling environment, and linkages to HIV testing, care, support & treatment to high risk groups .
- Needle syringe exchange program and opioid substitution therapy are to be provided
- Since the mode of transmission of Hepatitis B and Hepatitis C are largely similar to HIV/AIDS, NVHMU and SVHMU will coordinate with NACP for including prevention/management of hepatitis B and C in the package of prevention services for the key and bridge population.

Injection safety and infection control :

Targets WHO Regional Action Plan for Viral Hepatitis in South-East Asia : 2016-2021

By 2020, 50% of all injections are administered with safety engineered devices.

- Inadequate implementation of bio-medical waste management rules results in sharps injuries and increased risk of infections.
- States need to identify CBOs/NGOs and incentivise them for training on prevention of community barbers for HBV and HCV infections

National program for Surveillance of Viral Hepatitis :

- The initiative will undertake surveillance of acute, chronic hepatitis as well as their sequel over the next three years thereby estimating the disease burden for Hepatitis B and C in the country.

Diagnosis and Management of Viral Hepatitis with focus on treatment of Hepatitis B & C

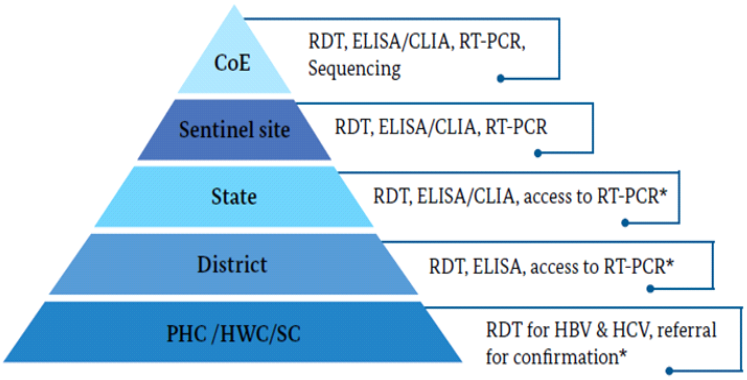
- The various components of service delivery under this head will include:

(a) Laboratory services; (b) Treatment services

Treatment Sites

- The services under this program will be delivered through the designated treatment sites that are located within an existing health facility, such as district hospitals and state medical colleges.
- There will be a few sites that will be labelled as Model Hepatitis Treatment centres (MTC) which will act as places for referral and mentoring of the other treatment centres (TC).

Network of Laboratories under the National Viral Hepatitis Control Program



**If samples are to be transported, they need to be collected, packaged and transported within six hours ofcollection under suitable environmental conditions.*

Clinical presentation :

Acute Hepatitis B :

Approximately 70 percent of patients with acute HBV infection have subclinical or anicteric hepatitis, while 30 percent develop icteric hepatitis. The disease may be more severe in patients co-infected with other hepatitis viruses or with underlying liver disease.

Fulminant hepatitis B is unusual, occurring in approximately 0.1 to 0.5 percent of patients; it is believed to be due to massive immune-mediated lysis of infected hepatocytes.

The rate of progression from acute to chronic hepatitis B in immunocompetent persons is determined primarily by the age at infection. The rate is approximately 90 percent for a perinatally acquired infection, 20 to 50 percent for infections between the age of one and five years, and less than 5 percent for an adult-acquired infection.

Chronic Hepatitis B (CHB)

A history of acute hepatitis is elicited in only a small percentage of patients with chronic HBV infection. In low or intermediate prevalence areas, approximately 30 to 50 percent of patients with chronic HBV infection have a past history of acute hepatitis; such a history is lacking in the remaining patients in these areas and in the majority of patients in high prevalence areas (predominantly perinatal infection).

Many patients with chronic HBV are asymptomatic (unless they have decompensated cirrhosis or have extrahepatic manifestations), while others have nonspecific symptoms such as fatigue. Some patients experience exacerbations of the infection which may be asymptomatic, mimic acute hepatitis, or manifest as hepatic failure.

Laboratory Investigations & Diagnosis :

Laboratory testing during the acute phase reveals elevations in the concentration of alanine and aspartate aminotransferase levels (ALT and AST); values up to 1000 to 2000 international units/L are typically seen during the acute phase with ALT being higher than AST. The serum bilirubin concentration may be normal in patients with anicteric hepatitis. The prothrombin time is the best indicator of prognosis. In patients who recover, the normalization of serum aminotransferases usually occurs within one to four months. A persistent elevation of serum ALT for more than six months

HBsAg	Anti-HBs	Anti-HBc	HBeAg	Anti-HBe	Interpretation
+	–	IgM	+	–	Acute hepatitis B , high infectivity *
+	-	IgG	+	-	Chronic hepatitis B , high infectivity *
+	-	IgG	-	+	1. Late acute or chronic hepatitis B, low infectivity 2. HBe Ag negative("precore- mutant") hepatitis B (chronic or rarely acute)
+	+	+	IgM	+/-	1. HBsAg of one subtype and heterotypic anti-HBs (common) 2. Process of seroconversion from HBsAg to anti-HBs (rare)
-	–	IgM	+/-	+/-	1. Acute Hepatitis B* 2. Anti-HBc "window"
-	-	IgG	-	+/-	1. Low level Hepatitis B carrier 2. Hepatitis B in remote past
-	+	IgG	-	+/-	Recovery from Hepatitis B
-	+	-	-	-	1. Immunization with HBsAg(after vaccination) 2. Hepatitis B in the remote past 3. False Positive

*IgM Anti-HBc may reappear during acute reactivation of chronic Hepatitis B

indicates a progression to chronic hepatitis.

Assessment and Staging of HBV Chronic infection:

Routine assessment of HBsAg-positive persons is needed to guide management and indicate the need for treatment. This generally includes assessment of:

1. Serological markers of HBV infection ;
2. Measurement of HBV DNA levels; and
3. Assessing severity of liver disease by - a. Liver enzymes b. Non-invasive tests (NITs) such as aspartate aminotransferase (AST)-to-platelet ratio index (APRI), FIB-4, transient elastography (FibroScan). c. Liver biopsy, if available

Serological markers of HBV infection :

Chronic Hepatitis B (CHB) infection is defined as the persistence of HBsAg for more than 6 months. Previous HBV infection is characterized by the presence of antibodies (anti-HBs and anti-HBc). Immunity to HBV infection after vaccination is characterized by the presence of only anti-HBs.

HBeAg: It also needs to be established whether the person is in the HBeAg-positive or HBeAg-negative phase of infection (please see the table above), though both require lifelong monitoring, as the condition may change over time. In persons with CHB, a positive HBeAg result usually indicates the presence of active HBV replication and high infectivity. Some HBeAg- negative persons have active HBV replication but are positive for anti-HBe and do not produce HBeAg due to the presence of HBV variants or pre-core mutants.

Measurement of HBV DNA levels :

Plasma HBV DNA concentrations quantified by real-time polymerase chain reaction (PCR) correlate with disease progression and are used to differentiate active HBeAg-negative disease from inactive chronic infection, and for decisions to treat and subsequent monitoring. HBV DNA concentrations are also used for optimal monitoring of response to antiviral therapy, and a rise may indicate the emergence of resistant variants.

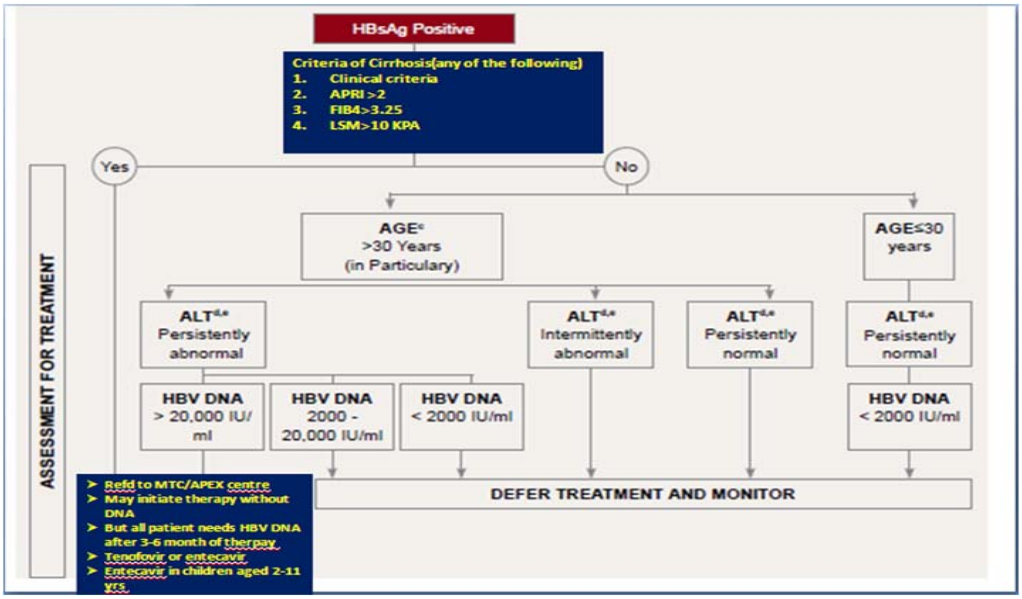
Assessing severity of liver disease :

A full assessment should include

- Clinical evaluation for features of cirrhosis and evidence of decompensation, and
- Measurement of serum bilirubin, albumin, ALT, AST, alkaline phosphatase (ALP), and prothrombin time; as well as full blood count, including platelet count.
- Other routine investigations include ultrasonography and alpha-fetoprotein (AFP) measurement for periodic surveillance for HCC, and endoscopy for varices in persons with cirrhosis.

Management aspects of Hepatitis – B :

Approach to a HBsAg positive patient



Whom to treat :

Chronic Hepatitis-B is defined as the persistence of HBsAg beyond 6 months. A repeat HBsAg testing after 6 months is done to confirm chronicity in those with acute hepatitis or a recent risk factor (180 days) for HBV infection and there is no necessity to confirm with a second HBsAg test in completely asymptomatic patients or those with features of fibrosis/cirrhosis/HBV flare.

The decision to treat a patient depends upon the presence of cirrhosis, fibrosis, levels of liver enzymes and platelet count. The HBeAg is not required for assessing the eligibility to initiate treatment and hence will not be used in the program.The persistently elevated ALT under the program is defined as at least 2 values

four weeks apart in the last 6 months, which are above the upper limit of normal.

The extent of fibrosis / cirrhosis can be established using several methods. APRI (AST-to-platelet ratio index) and FIB 4 are recommended as the preferred non-invasive tests (NIT) to assess for the presence of cirrhosis (APRI score >2: FIB 4 >3.25 in adults). The APRI score more than 1.5 or FIB-4 score more than 1.45 correlates with significant fibrosis (Stage F2). Transient elastography (eg, FibroScan) may be the preferred NITs in settings where they are available and cost is not a major constraint. A mean cut-off of e"12.5 kPa may be used to diagnose cirrhosis and e"8.0 to diagnose significant fibrosis.

PATIENT CATEGORY	PREFFERED DRUG
(1) All adults, adolescents and children aged 12 years or older	Tenofovir or Entecavir (as they have a high barrier to drug resistance)
(2) Woman of childbearing age	Tenofovir may be preferred in the eventuality of a pregnancy. Entecavir is not recommended in pregnancy
(3) Children aged 2–11 years.	Entecavir is recommended
(4) Age > 60 years; bone disease due to chronic steroid use or use of other medications that worsen bone density, history of fragility fracture, osteoporosis; altered renal function with eGFR<60 mL/min/1.73 m2 or albuminuria >30 mg/ 24 hr or moderate dipstick proteinuria or Low phosphate (<2.5 mg/dL) or in patient on hemodialysis	Entecavir may be preferred over Tenofovir
(5) Patients with reduced renal function or bone disease bone toxicities	TAF is the drug of choice. Entecavir is contraindicated
(6) Patients who have been exposed to lamivudine	Tenofovir is preferred as there is chance of entecavir resistance

Treatment :

What to treat with?

There are various antiviral agents recommended for treatment of CHB. The details are described in the National Treatment guidelines. However, the following table summarizes the recommendations:

Recommended drugs for the treatment of CHB and their doses in adults

Drug	Dose
Tenofovir disoproxil fumarate (TDF)	300 mg once daily
Entecavir (adult with compensated liver disease and lamivudine naive)	0.5 mg once daily
Entecavir (adult with decompensated liver disease)	1 mg once daily
Tenofovir alafenamide fumarate (TAF)	25 mg once daily

Selection of antiviral drug for CHB :

Drugs with a low barrier to resistance (lamivudine, adefovir or telbivudine) are available but not recommended as they lead to drug resistance.

The formulations for children are not currently approved, as and when they become available and approved, the above recommendation will be useful.

Monitoring the treatment :

The disease is complex and has sequelae, resolution as well as drugs side effects. Hence, three types of monitoring is necessitated:-

1) Monitoring for disease progression and treatment response in persons with CHB prior to, during and post-treatment

2) Monitoring for tenofovir or entecavir side-effects

3) Monitoring for hepatocellular carcinoma

Hepatitis B infection and pregnancy :

- Perinatal transmission is the most common route of HBV transmission.
- In the absence of prophylaxis, a large proportion of viraemic mothers, especially those who are seropositive for HBeAg, transmit the infection to their infants at the time of, or shortly after birth.
- The risk of perinatal infection is also increased if the mother has acute hepatitis B in the second or third trimester of pregnancy or within two months of delivery.
- Although HBV can infect the fetus in utero, this appears to be uncommon and is generally associated with antepartum hemorrhage and placental tears.
- The risk of developing chronic infection is 90%

following perinatal infection (up to 6 months of age) but decreases to 20–60% between the ages of 6 months and 5 years.

- All pregnant women with HBV should be evaluated for the need of treatment for hepatitis B and any associated liver disease, and given advice about prevention of transmission.
- Only a proportion of those with hepatitis B virus infection (pregnant or otherwise) need treatment.
- Hepatitis B in a pregnant woman is not a reason for considering termination of pregnancy.
- Similarly, the need for caesarean delivery should be decided based on obstetric indications, and not on the presence of HBV infection.
- Administration of hepatitis B vaccine to pregnant women with HBV provides no benefit either to the mother or the baby.

The goal of treatment in highly viremic mothers is to lower the serum HBV DNA level by several log10 IU/mL by the time of delivery to minimize the chance of newborn infection. The choice of antiviral agent is limited to those that are safe in pregnancy and include TDF, telbivudine, and lamivudine. These agents can be continued postpartum if necessary, but breastfeeding is not recommended in this setting.

Care of the baby :

Immunoprophylaxis of hepatitis B virus infection

- The newborn baby should be administered a timely first dose (the 'birth dose') of hepatitis B vaccine (monovalent) as soon as possible after birth, ideally within 24 hours and it will be better the earlier it can be administered.
- As HBIG is costly and has limited availability so under the program, HBIG will be made available and should be administered for preventing mother to child transmission of HBV (0.5 ml or 100 international units, intramuscular), this should be done as soon after birth as possible (and within 12-24 hours) and in anterolateral aspect of mid-thigh other than the one in which hepatitis B vaccine has been administered.

Breast-feeding :

A mother who has hepatitis B may breast-feed her baby, unless there is an exuding injury or disease of the nipple or surrounding skin. The advantages of breast-feeding far outweigh the risk, if any, of transmission of hepatitis B to a baby who has received hepatitis B vaccine.

Timing of testing :

If it is felt that the baby needs to be tested for hepatitis B, this should be done only after 1 year of age. Any positivity before this age is difficult to interpret and may resolve spontaneously over time.

Last but not the least -Prevention of HBV infection

- The risk of HBV infection may be higher in HIV-infected adults, and therefore all persons newly diagnosed with HIV should be screened for HBsAg and immunized if HBsAg is negative.
- Those already infected with HBV (HBsAg positive) do not benefit from HBV vaccine.
- PLHIV who have already suffered from HBV in the past and have developed protective titre of Anti-HBs antibody (>10 mIU/mL) also do not require HBV vaccine.
- Response to HBV vaccine is lower in persons with HIV or with a low CD4 count, and a meta-analysis has shown that a schedule of four double (40 ìg) doses of the vaccine provides a higher protective anti-HBs titre than the regular three 20 ìg dose schedule
- Besides this, all infants born to HBV positive women need to be immunized within 24 hours of birth (Dose - 0) followed by 6, 10 & 14 weeks (dose – 10 ìg IM) and HBIG – (0.5 ml or 100 international units, intramuscular), this should be done as soon after birth as possible (and within 12-24 hours) and in a limb other than the one in which hepatitis B vaccine has been administered.

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